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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/874,141	06/06/2001	Darrell Anderson	P 0280632 1995-30-0231CP2	6256

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EXAMINER	
GAMBEL, PHILLIP	
ART UNIT	**PAPER NUMBER**
1644	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/26/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/874,141	ANDERSON ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,3,5,16-21,23-27,30 and 33-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,3,5,16-21,23-27,30 and 33-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment, filed 11/6/06, has been entered.

Claims 22 and 28 have been canceled.
Claims 1, 4, 6-15, 29, 31 and 32 have been canceled previously.

Claims 2, 30 and 32-34 have been amended.

Claims 2, 3, 5, 16-21, 23-27, 30, and 33-38 are pending.

Applicant's election with traverse of multiple sclerosis (Group II-C) as the disease species has been acknowledged.

Claims 2, 3, 5, 16-21, 23-27, 30 and 33-38 as they read on treating multiple sclerosis with anti-gp39 antibodies are under consideration as the elected invention.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.
This Action will be in response to applicant's amendment, filed 11/6/06.
The rejections of record can be found in the previous Office Action.

Applicant's arguments and the examiner's rebuttal appear to be essentially the same of record.

3. Upon reconsideration, the previous objection under 35 U.S.C. 132 because it introduces new matter into the disclosure and the previous rejection under 35 U.S.C. 112, first paragraph, written description / new matter has been withdrawn.

4. Claims 2, 3, 5, 16-21 and 23-27, 30 and 33-39 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Black et al. (U.S. Patent No. 6,001,358) in view of the art known methods to screen for inhibitors of cytokines and proliferation in view of Schrader et al. (U.S. Patent No. 5,627,052), Burkly et al. (US2002/0028202 A1) and Wilson et al. (U.S. Patent No. 6,372,208 B1) essentially for the reasons of record
AND in further view of newly added Van den Eertwegh et al. (J. Exp. Med. 178: 1555-1565, 1993) and Roy et al. (J. Immunol. 151: 2497-2510, 1993) essentially for the reasons of record.

Applicant's arguments, filed 11/6/06, have been fully considered but are not found convincing essentially for the reasons of record.

Applicant's arguments and the examiner's rebuttal are essentially the same of record.

Applicant submits that the neither the combination of references nor the general knowledge of the ordinary artisan would have provided the suggestion or motivation to perform the claimed methods with an expectation of success.

Applicant's assertions concerning the reasonable expectation of screening soluble anti-human gp39 antibodies for their ability to *agonize* T cell proliferation and the production of the cytokines by $CD4^+$ T cells in vitro in the presence of immobilized anti-CD3 antibodies is somewhat confusing, given that the motivation and expectation of success in the prior art is based upon the ability of anti-gp39 antibodies (i.e. anti-CD40L antibodies) to inhibit or suppress CD40L:CD40-mediated interactions, not *agonize* such CD40L:CD40-mediated interactions, as apparently asserted by applicant.

Although the claims recite "*non-agonistic* of said human T cell activation response", both the claims as well as the prior art recognized and tested anti-gp39 antibodies (i.e. anti-CD40L antibodies) for their ability to inhibit CD40L:CD40-mediated interactions, including inhibiting $CD4^+$ T cell-mediated interactions, at the time the invention was made.

While applicant acknowledges the prior art teachings of blocking signals mediated via CD40L:CD40 interactions, applicant appears to limit the prior art to the individual teachings presented in each prior art reference, such as the prior art concerns with B cells and not with the effects of such blocking on the very target of the anti-gp39 antibodies (i.e., anti-CD40L antibodies), namely the gp39-expressing $CD4^+$ T cells and the nature of the signals by which said gp39-expressing $CD4^+$ T cells were known to operate (e.g., cytokines).

While applicant acknowledges that the prior art provided for testing the role of anti-gp39 antibodies (e.g. anti-CD40L antibodies) on antigen-presenting cells such as CD40-expressing B cells and dendritic cells, applicant continues to assert that no such motivation and expectation of success is provided in the prior art about testing the very target of the of the anti-gp39 antibodies (i.e., anti-CD40L antibodies), namely the gp39-expressing $CD4^+$ T cells and the nature of the signals by which said gp39-expressing $CD4^+$ T cells were known to operate (e.g., cytokines) and as taught and evidenced by the prior art of record.

As indicated previously, once a prima facie case of obviousness has been made the burden of going further is shifted to applicant. In re Keller, 208 USPQ 871, 882 (CCPA 1981). This applicant has not done, but rather argues the references individually and not their combination. One cannot show non-obviousness by attacking references individually where the rejections are based on a combination of references. In re Young, 150 USPQ 725 (CCPA 1968). See MPEP 2145.

Obviousness can be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine 5 USPQ2d 1596 (Fed. Cir 1988) and In re Jones 21 USPQ2d 1941 (Fed. Cir. 1992).

In this case, the teachings of the secondary references, including the previously added Van den Eertwegh et al and Roy et al. references, which clearly taught the importance of CD40 ligand expressing T cells and subsequent effector functions in the context of IL-2, IL-4 and γ-interferon, provided clear teachings of the known assays to test inhibitory antibodies, antibodies that inhibit T cell activation and proliferation, including antibodies that inhibit CD40 ligand:CD40 interactions.

As noted previously, Van den Eertwegh et al. (J. Exp. Med. 178: 1555-1565, 1993) and Roy et al. (J. Immunol. 151: 2497-2510, 1993) have been provided to make the record clear the CD40 ligand expressing cells involved in T – B cell interactions were associated and analyzed in the context of IL-2, IL-4 and interferon γ at the time the invention was made.

Also, Van den Eertwegh et al. teach evaluating or analyzing cytokine production associated with IL-2, IL-4 and interferon γ in the context of CD40 ligand- / gp39-expressing T cells in the context of T – B cell interactions in vitro and in vivo and that CD40L gp39 T cell and cytokine producing cell are simultaneously upregulated after immunization (e.g. see Discussion, including the last paragraph on page 1563) (see entire document, including Summary).

In addition, Roy et al. teach the regulation of gp39 / CD40 ligand on normal and cloned human $CD4^+$ T cells and the importance of the expression of CD40 ligand on activated T cells in determining effector function (see entire document, including the Discussion). Here, the studies were conducted with purified $CD4^+$ T cells and analysis of IL-2, IL-4 and interferon γ (e.g., see Materials and Methods and Results).

Therefore, it would have obvious to a person of ordinary skill in the art at the time the invention was made to apply the teachings of Van den Eertwegh et al. and Roy et al. to the teachings of Schrader et al., Burkly et al. and Wilson et al. as well as to those of Black et al. to screen and obtain antagonistic anti-gp39 antibodies with the ability to inhibit cytokines produced by activated T cells, including the inhibition of IL-2, IL-4 and γ-interferon, which were known to be products of the T cells targeted by antagonistic anti-gp39 antibodies, including purified $CD4^+$ T cells.

Van den Eertwegh et al and Roy et al. provided further evidence that the ordinary artisan understood the importance and role of CD40 ligand expressing T cells and cytokine production in the elaboration of immune response in the context of T-B cell interactions and subsequent effector functions. Note too, that human B cells were known antigen presenting cells at the time the invention was made.

Also, as noted previously, a person of ordinary skill in the art would have been motivated to produce this resultant ability of anti-gp39 antibodies to inhibit cytokine activity by activated T cells in order to test and select for those anti-gp39 antibodies that had the described properties of inhibiting gp39:CD40 interaction and the resultant ability of such antibodies to inhibit T cell mediated activation of immune response in the treatment of various conditions and disorders, including multiple sclerosis.

Both Black et al. and Wilson et al. teach inhibitory anti-CD40 ligand (anti-gp39) antibodies and their effects on T cell mediated activation and functions.

Given the role of various cytokines such as IL-2, IL-4 and γ-interferon, which were known to be products of the T cells targeted by antagonistic anti-gp39 antibodies, play in immune responses, one of ordinary skill in the art would have been motivated to screen and test for the properties of antagonistic anti-CD40 ligand antibodies that inhibited T cell activation and proliferation in the selection of such inhibitory antibodies that can regulate the various manifestations of T cell activation and function.

The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983). See MPEP 2144.

Applicant's arguments have not been found persuasive.

Again, the following of record is reiterated for applicant's convenience.

Black et al. teach methods of treating disease condition wherein gp39 inhibition is therapeutically beneficial (columns 13-14 and 31-34), including multiple sclerosis with column 14, line 40 and column 32, line 67) with antibodies that bind gp39 (CD40 ligand), which block signals delivered via CD40 (See Examples 2, 3 columns 22-23; Examples 11-17 on columns 28-38 (see entire document).

In addition, Black et al. teach chimeric, humanized, and primatized antibodies, including the use of different heavy chain constant regions (IgG1, IgG3, IgG4), with conservative amino acid substitutions such as Kabat positions 229 and 236 as well as the 24-31 antibody specificity and its variable regions amino acid sequences encompassed by the claimed methods (see entire document, including Background of the Invention, including columns 6-7; Summary of the Invention; Detailed Description of the Invention, including columns 13-22; Claims). Further, it is noted that Black et al. teach that it was known that $gp39^+$ T cells produced IL-2, IL-4 and ϒ-interferon (see column 4, paragraph 1). In addition, Black et al. teach modes of administration and dosages of antagonistic anti-gp39 antibodies encompassed by the claimed methods (see columns 33-38).

Again as noted above, applicant asserts that Black et al. does not describe or suggest a method of obtaining anti-gp39 antibodies that includes steps of assaying for and identifying non-agonistic antibodies with the characteristics of human T cell activation.

While applicant has relied upon the teachings of Blair et al. (J. Exp. Med. 191: 651-660, 2000) and Blotta et al. (J. Immunol. 156: 3133-3140. 1996) to indicate the agonistic properties of anti-gp39 antibodies on T cells,
it was noted that these references appear to rely upon the cross-linking of anti-gp39 antibodies to achieve such agonistic properties.

While applicant has also relied upon the data in Table 5 of Black and the possible distinctions between anti-mouse gp39 antibodies versus anti-human gp39 antibodies to support the unobviousness of the prior art rejection,
it has been pointed out that both Black et al. and Wilson et al. teach inhibitory anti-CD40 ligand (anti-gp39) antibodies and their effects on T cell mediated activation and functions and that Wilson et al. makes no distinction between inhibitory anti-mouse gp39 antibodies versus anti-human gp39 antibodies.

Black et al. differs from the claimed methods by not disclosing the art known use of screening for inhibitors of cytokine activity such as IL-2, IL-4 and ϒ-interferon as well as cell proliferation per se in selecting antagonistic anti-gp39 antibodies.

Schrader et al. teach methods of producing antibodies of a desired function to a variety of antigens, including IL-2 and ϒ-interferon, including the section of antibodies that neutralizes a growth factor or detection of antibodies that neutralize IL-2 (e.g. see columns 8-9, overlapping paragraph) and exemplifies the detection of antibodies that neutralize IL-2 (see Example 1 on columns 21-22) (see entire document, including Summary of the Invention and Detailed Description of the Invention).

Burkly et al. teach known methods of assaying or screening the ability of antagonists such as antibodies to block a response to a particular cytokine (e.g. IL-2) (See GC Chain Blocking Agents and Production of GC Blocking Antibodies on pages 7-8 and Testing Compounds of the Invention for Biological Utility on page 13). Burkly et al. note that it will be recognized by one skilled in the art, that these screens can be arranged to discover antibodies whose activities are conspicuous in one or more of these assays (see paragraph 095 on page 8) and that one of skill in art may easily determined using well known methods whether a particular blocking agent displays biological activity (see Testing Compounds of the Invention for Biological Utility on page 13).

Wilson et al. teach that CD40 ligand – CD40 interactions are desirable given its broad activity in both T helper cell activation and function as well as the absence of redundancy in its signaling pathway (see entire document, particularly column 6, paragraphs 4-5). In addition, Example 8 describes analyzing the effect of CD40 ligand blockade with antibodies on T cell activation using both in vitro and in vivo assays, including T cell proliferation (see columns 20-22).

While applicant appears to focus on the vivo testing aspects of the teachings of Wilson et al., the combined references, including Wilson et al. of record and the newly added Van den Eertwegh et al and Roy et al. which clearly provide for the importance of CD40 ligand expressing T cells and subsequent effector functions in the context of IL-2, IL-4 and γ-interferon provide clear teachings of the known assays to test inhibitory antibodies, antibodies that inhibit T cell activation and proliferation, including antibodies that inhibit CD40 ligand : CD40 interactions.

Therefore, it would have obvious to a person of ordinary skill in the art at the time the invention was made to apply the teachings of newly added Van den Eertwegh et al and Roy et al. to those of Schrader et al., Burkly et al. and Wilson et al. as well as to those of Black et al. to screen and obtain antagonistic anti-gp39 antibodies with the ability to inhibit cytokines produced by activated T cells, including the inhibition of IL-2, IL-4 and γ-interferon, which were known to be products of the T cells targeted by antagonistic anti-gp39 antibodies. According to Black et al., a person of ordinary skill in the art would have been motivated to produce this resultant ability of anti-gp39 antibodies to inhibit cytokine activity by activated T cells in order to test and select for those anti-gp39 antibodies that had the described properties of inhibiting gp39:CD40 interaction and the resultant ability of such antibodies to inhibit T cell mediated activation of immune response in the treatment of various conditions and disorders, including multiple sclerosis. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments have not been found persuasive.

5. No claim allowed.

6. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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